I. THE SYNTHESIS OF 14-AZAPERHYDROCYCLOPENTENOPHENANTHRENES

II. THE SYNTHESIS OF 6-METHYL-1-AZABICYCLO[5.3.0]DECANE

III. THE REARRANGEMENT OF 3-KETO-1-AZABICYCLO[5.4.0]HENDECANE

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ERNEST D. NICOLAIDES

B.S., Monmouth College, 1948
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ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to Professor Nelson J. Leonard for suggesting these problems, and for his invaluable advice and encouragement given throughout their progress.

He also wishes to thank the University of Illinois for a Research Assistantship held during the academic year 1950-51, with funds provided by a Grant-in-Aid from E. I. duPont de Nemours and Company, Inc.

PART ONE

THE SYNTHESIS OF 14-AZAPERHYDROCYCLOPENTENOPHENANTHRENES

Introduction

Although the preparation of several basic and heterocyclic steroids has been reported,[1] there is no record of the synthesis of a steroid containing nitrogen in its skeleton structure. The present investigation was carried out in an attempt to synthesize a steroid-type hormone containing a nitrogen atom in the fourteen position of the molecule.

Discussion Of Results

The synthesis of a steroid containing nitrogen in the fourteen position has been accomplished. The condensation of benzo(f)quinaldine with ethyl oxalate produced ethyl β-(3-benzo(f)quinoline)-pyruvate. Hydrogenation of this pyruvate ester over copper chromite catalyst at 265° and 300 atm. resulted in the formation of 14-azaperhydrocyclopentenophenanthrene. The identity of the product was established by analogy with other similar reductive cyclizations[2] and by analysis of the amine and its derivatives.

The synthesis of a second steroid containing nitrogen in the fourteen position was attempted, but the unreactivity of 3-carbethoxybenzo(f)octahydroquinoline resulted in the failure of the synthesis.

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PART TWO

THE SYNTHESIS OF 6-METHYL-1-AZABICYCLO[5.3.0]DECANE

Introduction

The condensation of methyl γ-nitrobutyrate with methyl sorbate has been found to yield a compound identified as either the 1,4 or the 1,6 Michael addition product.[1a] Hydrogenation of this condensation product gave a tertiary amine which was shown to be either 1-*n*-propylpyrrolizidine or 6-methyl-1-azabicyclo[5.3.0]decane. The possibility of the product being 1-*n*-propylpyrrolizidine was partially eliminated by the unequivocal synthesis of this compound.[1b] In the present work, the unequivocal synthesis of 6-methyl-1-azabicyclo-[5.3.0]decane was carried out in order to establish definitely the identity of the hydrogenated condensation product.

Discussion Of Results

The synthesis of 6-methyl-1-azabicyclo[5.3.0]decane was similar to the method of Prelog[2] as modified by Leonard and Wildman[3] used in the preparation of azabicyclo compounds. 1-Bromo-4-(*p*-methoxyphenoxy)-butane was condensed with ethyl cyanoacetate and the resulting product was then alkylated with methyl iodide. The substituted caproic ester was saponified to the acid and then decarboxylated, giving 1-(*p*-methoxyphenoxy)-5-cyanohexane. This nitrile was caused to react with the Grignard reagent prepared from γ-ethoxypropyl bromide and gave a ketone, 1-ethoxy-9-(*p*-methoxyphenoxy)-5-methyl-4-nonanone. The ketone was hydrogenated in liquid ammonia to the corresponding amine. The terminal ether linkages of the amine were cleaved with hydrogen bromide and the resulting dibromoamine hydrobromide was cyclized in dilute sodium hydroxide solution to 6-methyl-1-azabicyclo[5.3.0]decane. The infrared absorption spectrum of the picrate of the product was identical with the infrared absorption spectrum of the picrate of the hydro-

genated condensation product.

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PART THREE

THE REARRANGEMENT OF 3-KETO-1-AZABICYCLO[5.3.0]HENDECANE

Introduction

It has been established that the Clemmensen reduction of a monocyclic seven-membered α-aminoketone[1] and a bicyclic α-aminoketone possessing fused five- and seven-membered rings[2] results in the contraction of the ketonic ring and expansion of the non-ketonic ring. The present study was undertaken in order to determine the product obtained from the Clemmensen reduction of a bicyclic α-aminoketone possessing fused six- and seven-membered rings.

Discussion Of Results

The Clemmensen reduction of 3-keto-1-azabicyclo[5.4.0]-hendecane would be expected to yield 4-methylquinolizidine. The two racemates of 4-methylquinolizidine were obtained by the catalytic hydrogenation of 1-(2′-pyridyl)-4-pentanone,[3] and were separated by fractional distillation. The efficiency of separation was followed by determination of the infrared absorption spectra. 3-Keto-1-azabicyclo[5.4.0]hendecane was synthesized as follows. Diethyl β-(2-pyridyl)-ethylmalonate

was converted to 1-carbethoxymethyl-2-(γ,γ-dicarbethoxypropyl)-pyridinium bromide by treatment with ethyl bromoacetate. Hydrogenation of this quaternary salt, followed by hydrolysis, decarboxylation and then reësterification produced diethyl piperidyl-1-acetate-2-γ-butyrate which was cyclized to 3-keto-1-azabicyclo[5.4.0]hendecane by a Dieckmann ring closure.

Clemmensen reduction of the γ-aminoketone gave a tertiary amine which was separated into two isomers by careful distillation. The infrared absorption spectrum of one of the isomers was found to be identical with the infrared absorption spectrum of isomer "A" of 4-methylquinolizidine, and the second isomer had a spectrum identical with the spectrum of isomer "B" of 4-methylquinolizidine.

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VITA

The author was born in Monmouth, Illinois, on September 11, 1924. He attended elementary and high schools in that city and was graduated from Monmouth High School in 1942. After serving in the Army Air Corps from 1943 to 1946, he entered Monmouth College and in August of 1948 he received the degree of Bachelor of Science in Chemistry. He entered the Graduate College of the University of Illinois in September, 1948 and received the Master of Science degree from that institution in 1949. He held a Research Assistantship during the academic year 1950-51.